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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/600,623	06/20/2003	Uri H. Saragovi	OGIL-002 US	7195

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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/600,623	SARAGOVI ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29 and 31-34* is/are pending in the application.

4a) Of the above claim(s) *1-29 and 31-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35 and 39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/01/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to the Amendment

The Amendment filed on 3/01/2007 in response to the previous Non-Final Office Action (9/01/2006) is acknowledged and has been entered.

Claims 1-29, 31-35 and 39 are pending.

Claims 1-29 and 31-34 are withdrawn from consideration as being drawn to non-elected inventions.

Claims 35 and 39 are currently under consideration.

The Declaration under 37 CFR 1.132 filed on 3/01/2007 by Mark Greene is insufficient to overcome the rejection of claim 39 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description as set forth in the last Office action because: the declaration does not appear to be commensurate in scope with the rejection. For example, the Declaration sets forth (page 2) that considering the routine-art recognized method of making antibodies to fully characterized antigens, the well known structural characteristics of antibodies, the functional characteristics of antibody binding and the fact that the antibody technology is well-developed and mature, one of skill in the art would have recognized that the spectrum of monoclonal antibodies which bind to p75, TrKA and IGF-IR polypeptide were implicitly disclosed in the specification. However, the Examiner recognizes that the claim 39 is not drawn to a genus of monoclonal antibodies which bind to p75, TrKA and IGF-IR polypeptide, but recite specific monoclonal antibodies. In this case, as noted in the previous office action, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics.

[FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3rd ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species.

Information Disclosure Statement

The Information Disclosure Statement filed on 3/01/2007 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. A signed copy of the IDS is attached hereto.

Rejections Withdrawn:

The rejection of claims 35 and 38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement are withdrawn in view of Applicants amendments and arguments thereto.

The rejection of claims 35 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description has been withdrawn in view of Applicants amendments.

The rejection of claim under 35 U.S.C. 102(b) as being anticipated by Trail et al. (Clinical Cancer Research 1999; 5: 3632-3638, IDS) as evidenced by Willner et al. (Bioconjugate Chem. 1993; 4: 521-527) and Dietro et al. (Braz. J. Med. Biol. Res. 1999; 32; 925-939, *of record*) is withdrawn in view of Applicants amendments.

Rejections Maintained:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 39 remains rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description.

It is unclear whether a cell line which produces an antibody having the exact chemical identity of α-IR3, 5C3 or MC192 is known or publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one or ordinary skill in the art could not be assured of the ability to practice the claimed invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3rd ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See, 37 CFR 1.808.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made at an acceptable depository and that the following criteria have been met:

(a) during the pendency of this application, access to the invention will be afforded to one determined by the Commissioner to be entitled thereto;
(b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon granting of the patent;
(c) the deposit will be maintained for a term of at least thirty (30) years and at least five (5) years after the most recent request for the furnishing of a sample of the deposited material;
(d) a viability statement in accordance with the provisions of 37 CFR 1.807; and
(e) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an addition means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If a deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundack, 773 F.2d. 1216, 227 USPQ 90 (CAFC) and 37 CFR 1.801-1.809 for further information concerning deposit practice.
In addition the identifying information set forth in 37 CFR 1.809(d) should be added to the specification. See 37 CFR 1.803 - 37 CFR 1.809 for additional explanation of these requirements.

In response to this rejection, Applicants assert that claim 39 meets the requirements for enablement of antibody-based compositions in view of the Federal Circuit's holdings regarding monoclonal antibody compositions differ from other areas of biotechnology such as recombinant DNA. That is, Applicants assert, the Court has found monoclonal antibody compositions (In re Wands, 858 F.2d 731, 733-734 (Fed. Cir. 1988)), unlike genes or DNA molecules, to be enabled by a specification that describes them by their function without structural description. Like Wands,

Applicants assert that the monoclonal antibodies which bind to p75, TrKA and IGF-1R polypeptides can be made with a high rate of success from readily available starting materials without undue experimentation. As detailed in the Greene Declaration, Applicants assert that the level of skill and knowledge of skill in the art of antibodies at the time of filing was such that production of antibodies against a well-characterized antigen was conventional. As such, Applicants assert that amended claims 35 and 39 are in condition for allowance as they are in compliance with the enablement requirement of 35 USC 112, 1st paragraph, because at the time of filing one of skill in the art would know how to make the invention now claimed.

These arguments have been carefully considered, but are not found persuasive.

In the instant case, the Examiner acknowledges and agrees with Applicants that the level of skill and knowledge of skill in the art of antibodies at the time of filing was such that production of antibodies against a well-characterized antigen was conventional. As such, one of ordinary skill in the art could make and use monoclonal antibodies, in general, specific for p75, TrKA and IGF-1R. However, the Examiner recognizes that claim 39 recites a specific monoclonal antibodies which the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description. As noted above, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3rd ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species. As such, the rejection is maintained.

New Rejections Necessitated by further Consideration:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 35 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Saragovi et al. (WO 97/21732, 1997, IDS) in view of Webb et al. (US 6,652,864, filed on 12/21/19980 and Shin et al. (Cancer Immunol. Immunother. 1994; 38: 92-98).

Saragovi et al. teach a method of treating a neoplastic tumor which expresses TrKA receptors in a patient comprising administering an effective amount of an antibody or functional fragment thereof (page 4, lines 8-14). With regards to the antibody, the WO document teaches that the antibody includes, but is not limited to, monoclonal antibody 5C3 (page 7, lines 6+). Moreover, the WO document teaches that the method of treating a tumor further comprises coupling a cytotoxic agent to the antibody and administering to said a patient the coupled antibody (page 5, lines 8-14).

Saragovi et al. do not explicitly teach that the coupled antibody has the formula W-Z-X, wherein X is a chemotherapeutic agent selected from the group consisting of doxorubicin and paclitazel, W is the monoclonal antibody, 5C3, and z is a breakable linker which covalently links W and X.

Webb et al. teach a compound having the formula B-L-M, wherein B is a binding agent capable of selectively binding to a nerve cell surface receptor, M is a moiety and L is a linker which couples L to M (column 2, lines 3-14). In particular, the patent teaches that the binding agents are antibodies including, but not limited to, monoclonal antibodies 5C3 and anti-human p75 monoclonal antibody MC192 (column 2, lines 56-60). Moreover, the patent teaches that linker is a cleavable linker which enables the moiety M linked to the binding agent B to be released from the compound once absorbed by the nerve cell (column 3, liens 16-20).

Shih et al. teach that the major limitation of conventional cancer chemotherapy is the non-selectivity of this treatment, wherein the maximum tolerated dose that a patient can receive is often lower than is necessary for tumor destruction (page 92, 2nd column, 1st paragraph). As such, Shin et al. teach a doxorubicin immunoconjugate, e.g., doxorubicin conjugated to an anti-CEA antibody, which exhibited substantially increased tumorcidal effects over those of the unconjugated doxorubicin in the tumor system that has been resistant to most of the available chemotherapeutic

agents, and revealed minimal host toxicity when compared to an equivalent dose of the free drug, e.g., unconjugated doxorubicin (page 92, 2nd column, 2nd paragraph).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the coupled antibody as taught by Saragovi et al. to include a cleavable linker between the antibody and cytotoxic antibody in view of the teachings of Webb et al. One would have been motivated to do so because Webb et al. teach that the incorporation of a cleavable linker between the binding agent and moiety enables the moiety to be released once absorbed by the nerve cell, e.g., TrKA receptor. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by modifying the coupled antibody as taught by Saragovi et al. to include a cleavable linker between the antibody and cytotoxic antibody in view of the teachings of Webb et al., one would achieve a method of treating a tumor, wherein the cytotoxic agent is released from 5C3 within the tumor.

Moreover, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the coupled antibody as taught by Saragovi et al. to include doxorubicin as the cytotoxic moiety in view of the teachings of Shih et al.. One would have been motivated to do so because Shih et al. teach the major limitation of conventional cancer chemotherapy is the non-selectivity of this treatment, wherein a doxorubicin immunoconjugate exhibited substantially increased tumorcidal effects over those of the unconjugated doxorubicin in the tumor system. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by modifying the coupled antibody as taught by Saragovi et al. to include doxorubicin as the cytotoxic moiety in view of the teachings of Shih et al., one would achieve a method of reducing the major limitation of non-selectivity of doxorubicin treatment.

Therefore, NO claim is allowed

All other rejections and/or objections are withdrawn in view of applicant's amendments and arguments there to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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